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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/782,361 | 02/13/2001 | Yu-Wen Hu | 4757US | 1070 |

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EXAMINER

STRZELECKA, TERESA E

ART UNIT

PAPER NUMBER

1637

DATE MAILED: 01/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| | | | |
|------------------------------|------------------------|---------------------|--|
| Office Action Summary | Application No. | Applicant(s) | |
| | 09/782,361 | HU, YU-WEN | |
| | Examiner | Art Unit | |
| | Teresa E Strzelecka | 1637 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 28 October 2003.
- 2a) This action is **FINAL**. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-12, 14, 15 and 17-26 is/are pending in the application.
 - 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) 1-12, 14, 15, 17-19 and 23 is/are allowed.
- 6) Claim(s) 20-22 and 24-26 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on 28 October 2003 is/are: a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 - a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 13) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
 - a) The translation of the foreign language provisional application has been received.
- 14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

| | |
|--|--|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ . |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. This office action is in response to an amendment filed on October 28, 2003. Claims 1-12, 14, 15 and 17-26 were previously pending. Applicant amended claims 1 and 17-26. Claims 1-12, 14, 15 and 17-26 are pending and will be examined.
2. Applicant's amendments and arguments overcame the following: objection to claims 1 and 20; rejection of claims 1-11, 14, 15, 17-19 and 23 under 35 U.S.C. 102/103 over Fahy and Lundberg et al; rejection of claim 12 under 35 U.S.C. 103 over Fahy, Lundberg et al. and Resnick et al.; rejection of claim 12 under 35 U.S.C. 103 over Fahy, Lundberg et al. and Okamoto et al. Rejections of claims 20-22 and 24-26 are maintained for reasons given in the "Response to Arguments" section.

Drawings

3. The drawings are objected to because the newly submitted Figure 1 does not contain SEQ ID NOs which were present in the original drawing. A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Response to Arguments

4. Applicant's arguments filed October 28, 2003 have been fully considered but they are not persuasive. Applicant argues that "... neither Fahy nor Lundberg, alone or in combination, clearly defines where extension termination will occur. That is to say, Fahy and Lundberg do not describe termination of extension when mispairing occurs "within a 2 to 4 base pair range located downstream of the 3' end of the primer" or "at at least one of a first or second base pair immediately adjacent to the 3' end of the primer". Fahy and Lundberg therefore do not and cannot lead an

ordinarily skilled artisan to ascertain the specific site of termination relative to the 3' end of the primer, as recited in the subject claims" (page 15 of the Response, second paragraph).

However, while Applicant did show that the primer extension is terminated when two or more mispairs occur during primer extension and that Pfu polymerase can in fact extend past single mispaired base pairs within several nucleotides from the 3' end of the primer, which is an unexpected result, the fact that primer extension is terminated when a mispaired nucleotide is immediately adjacent to the 3' end of the primer would be expected from Pfu polymerase, which has 3'-> 5' polymerase activity.

The rejections are maintained.

Claim Rejections - 35 USC § 102/103

5. Claims 20-22 and 24-26 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Fahy (WO 96/30545; previously cited) and Lundberg et al. (Gene, vol. 108, pp. 1-6, 1991; previously cited).

Regarding claims 20-22 and 24-26, Fahy teaches a method of simultaneous determination of related polynucleotide sequences, for example, within the same gene, in a nucleic acid sample by:

- providing a nucleic acid sample from a patient (page 29, lines 17-37; page 30, lines 1-30),
- extending a primer specific for the genotype by Pfu (= pfu) DNA polymerase (page 19, lines 36, 37; page 20, lines 3-34), and an incomplete set of dNTP's (at most three) in the absence of ddNTPs (page 7, lines 18-37; page 18, lines 26-32), where the primer is labeled with fluorescent label (page 8, lines 12-14),
- characterizing the extension products by separating the extension products based on their lengths (page 21, lines 2-14; Fig. 5A-C),

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- analyzing the characterized extension products based on primer-specific pairing and non-specific pairing to determine genotype of the extended nucleic acid sequence and generating a genotype-specific extension profile of the extension products (page 34, lines 26-37; page 35, lines 1-11; Table IA and IB; Fig. 8; Fig. 4A and 4B).

B) Regarding claims 20 and 24, Fahy does not teach termination of extension products in the presence of a mispair occurring at at least one of a first or second base pair immediately adjacent to the 3' end of the primer. However, the position of a mispair formation with respect to the 3' end of the primer is dependent on the template sequence and type of dNTPs present in the reaction mixture, and is inherently related to the fact that Pfu polymerase is a high-fidelity polymerase.

C) The preceding rejection is based on judicial precedent following In re Fitzgerald, 205 USPQ 594, because Fahy et al. is silent with respect to the fact that Pfu polymerase terminates primer extension at a distance determined by the type on dNTPs present in the reaction and template sequence. However, termination of extension products in the presence of a mispair occurring at at least one of a first or second base pair immediately adjacent to the 3' end of the primer recited in claims 20 and 24 are deemed to be inherent in the property of the high-fidelity in the Pfu polymerase in Fahy (page 20, lines 3-34) because of teachings of Lundberg et al., described below.

Lundberg et al. teach testing proofreading ability of Pfu polymerase by extension of a primer with one, two or three mismatches at the 3' end of the primer. All of the primers were extended and mismatched nucleotides were excised by the 3'->5' exonuclease activity of the polymerase (Fig. 1; page 2, paragraph (b)). Following Figure 1b, it is clear that if only dTTP and dGTP, for example, were included in the reaction mixture, mispair would have occurred at the second base from the 3' end of the primer, and extension would have been terminated there. If only dTTP and dCTP, for example, were included in the reaction mixture, mispair would have occurred at the third base from

the 3' end of the primer, and extension would have been terminated at this position. If only dTTP and dATP, for example, were included in the reaction mixture, mispair would have occurred at the second and third base from the 3' end of the primer, and extension would have been terminated there.

D) In the alternative, it is obvious that termination of primer extension at a certain distance from the 3' end of the primer is an inherent property of the Pfu DNA polymerase under reaction conditions where an incomplete set of dNTPs is present in the reaction mixture. Fahy teaches the high-fidelity of the Pfu polymerase (page 20, lines 3-34) and Lundberg et al. teach testing the proofreading ability of Pfu polymerase by extension of a primer with one, two or three mismatches at the 3' end of the primer. All of the primers were extended and mismatched nucleotides were excised by the 3'->5' exonuclease activity of the polymerase (Fig. 1; page 2, paragraph (b)). Following Figure 1b, it is clear that if only dTTP and dGTP, for example, were included in the reaction mixture, mispair would have occurred at the second base from the 3' end of the primer, and extension would have been terminated there. If only dTTP and dCTP, for example, were included in the reaction mixture, mispair would have occurred at the third base from the 3' end of the primer, and extension would have been terminated at this position. If only dTTP and dATP, for example, were included in the reaction mixture, mispair would have occurred at the second and third base from the 3' end of the primer, and extension would have been terminated there.

Therefore it would have been obvious to one of ordinary skill in the art at the time of the invention that Pfu polymerase would have terminated primer extension at different positions relative to the 3' end of the primer in a fashion dependent on the template sequence and type of dNTPs included in the incomplete dNTP set. The termination would occur because Pfu possesses proofreading function.

The burden is on applicant to show that termination of extension products in the presence of a mispair occurring at at least one of a first or second base pair immediately adjacent to the 3' end of the primer is either different or non-obvious over that of Fahy.

6. No references were found teaching or suggesting claims 1-12, 14, 15, 17-19 and 23. Claims 1-12, 14, 15, 17-19 and 23 are allowed. Applicant showed an unexpected result of primer extension of mispaired single base pairs by Pfu polymerase and termination of the extension when two or more mispairs are encountered by the polymerase.

Conclusion

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E Strzelecka whose telephone number is (571) 272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached at (703) 308-1119. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

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Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Gary Benzion will move to the new office on January 22, 2004. His new phone number is (571) 272-0782.

TS
January 21, 2004



JEFFREY FREDMAN
PRIMARY EXAMINER